Effects of the poly(ethylene glycol) hydrogel crosslinking mechanism on protein release.

Journal: Biomater Sci

Publication Year: 2015

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PubMed link: 26539660

Funding Grants: Autologous iPSC Therapy for Urinary Incontinence

Public Summary:
Matrix stiffness has been shown to play an important role in modulating various cell fate processes such as differentiation and cell cycle. Given that the stiffness can be easily tuned by varying the crosslinking density, poly(ethylene glycol) (PEG) hydrogels have been widely used as an artificial cell niche. However, little is known about how changes in the hydrogel crosslinking density may affect the accumulation of exogenous growth factors within 3-D hydrogel scaffolds formed by different crosslinking mechanisms. To address such shortcomings, we measured protein diffusivity and accumulation within PEG hydrogels with varying PEG molecular weight, concentration and crosslinking mechanism. We found that protein accumulation increased substantially above a critical mesh size, which was distinct from the protein diffusivity trend, highlighting the importance of using protein accumulation as a parameter to better predict the cell fates in addition to protein diffusivity, a parameter commonly reported by researchers studying protein diffusion in hydrogels. Furthermore, we found that chain-growth-polymerized gels allowed more protein accumulation than step-growth-polymerized gels, which may be the result of network heterogeneity. The strategy used here can help quantify the effects of varying the hydrogel crosslinking density and crosslinking mechanism on protein diffusion in different types of hydrogel. Such tools could be broadly useful for interpreting cellular responses in hydrogels of varying stiffness for various tissue engineering applications.

Scientific Abstract:
Poly(ethylene glycol) (PEG) hydrogels are widely used to deliver therapeutic biomolecules, due to high hydrophilicity, tunable physicochemical properties, and anti-fouling properties. Although different hydrogel crosslinking mechanisms are known to result in distinct network structures, it is still unknown how these various mechanisms influence biomolecule release. Here we compared the effects of chain-growth and step-growth polymerization for hydrogel crosslinking on the efficiency of protein release and diffusivity. For chain-growth-polymerized PEG hydrogels, while decreasing PEG concentration increased both the protein release efficiency and diffusivity, it was unexpected to find out that increasing PEG molecular weight did not significantly change either parameter. In contrast, for step-growth-polymerized PEG hydrogels, both decreasing PEG concentration and increasing PEG molecular weight resulted in an increase in the protein release efficiency and diffusivity. For step-growth-polymerized hydrogels, the protein release efficiency and diffusivity were further decreased by increasing crosslink functionality (4-arm to 8-arm) of the chosen monomer. Altogether, our results demonstrate that the crosslinking mechanism has a differential effect on controlling protein release, and this study provides valuable information for the rational design of hydrogels for sophisticated drug delivery.